

Osteopenia and osteomalacia after gastrectomy: interrelations between biochemical markers of bone remodelling, vitamin D metabolites, and bone histomorphometry

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Abstract

The prevalence of metabolic disease in a population of 68 postgastrectomy patients was assessed using histomorphometric evaluation of transiliac bone biopsy specimens after tetracycline double labelling. Trabecular bone volume was significantly lower in the postgastrectomy group ($p < 0.01$): 62% of the patients had increased osteoid surface, 56% increased osteoid thickness, and 24% increased mineralisation lag time. Only 18%, however, fulfilled the diagnostic criteria for osteomalacia – increased osteoid thickness and increased mineralisation lag time. Postgastrectomy patients had reduced serum concentrations of calcium ($p < 0.01$), phosphate ($p < 0.01$), and 25-hydroxyvitamin D, while levels of alkaline phosphatase and 1,25 dihydroxyvitamin D were high ($p < 0.01$). The severity of the mineralisation defect as reflected by mineralisation lag time was positively correlated to serum 25-hydroxyvitamin D, but unrelated to serum 1,25-dihydroxyvitamin D. Multiple linear regression analysis showed that serum 25-hydroxyvitamin D, age, and the duration of postoperative follow up were significant determinants of the mineralisation defect in a given patient. The limited value of serum markers in the diagnosis of osteomalacia was emphasised by the fact that six of the eight patients with osteomalacia had normal serum levels of calcium and alkaline phosphatase, and five of the eight had values for 25-hydroxyvitamin D in the normal range for healthy control subjects. The results clearly show the need for vitamin D supplementation and regular control after gastric resection.

osteoid width, or both, as has been the case in most previous papers,^{9–12} other metabolic bone diseases, such as myxoedema and secondary hyperparathyroidism, may be included.^{13,14}

Recently, the stereological methods for estimating the three dimensional thickness in histological sections have been improved,¹³ making the estimates more reproducible and accurate. The aim of this study therefore was to assess the occurrence of osteomalacia in a group of postgastrectomy patients using these new methods and more stringent definitions of osteomalacia. Moreover, we wanted to evaluate the relative contribution of changes in vitamin D metabolites, age, and the duration of the postoperative observation period in the occurrence of osteomalacia.

Methods

We studied 68 patients, 45 men and 23 women, who had had total or partial gastrectomy for peptic ulcer disease. Thirty nine patients, aged 41–70 years (31 men and 8 women, mean age 58 years), had previously undergone polya-gastrectomy (average postoperative follow up 17 years, range 6–31 years) and 24 patients (11 men and 13 women, aged 34–87 years, mean 58 years) had had a Billroth I resection (average postoperative follow up 9 years, range 4–28 years). Five patients, aged 45–75 years (three men and two women, mean age 60), who had undergone total gastrectomy, were also included (average postoperative follow up five years). Only 60 patients had all biochemical variables determined. Forty patients took one multivitamin tablet (400–600 IU vitamin D) every day, but no other medication known to influence bone and calcium homeostasis was taken by any of the patients in the study.

The age and sex matched control subjects used to compare the histomorphometric studies comprised 41 healthy volunteers, who had undergone bone biopsy after tetracycline double labelling.¹⁴ To compare biochemical indices normal subjects matched by age and sex were chosen from a large number of subjects investigated in the Department of Clinical Chemistry, Aarhus Amtssygehus. The vitamin D metabolites in patients were compared to results in a sex and age matched control group obtained from the laboratory where the assay was performed.¹⁵ Matching took into account the time of year for the investigation (November–April).

Several studies have reported osteopenia and an increased incidence of skeletal fractures in partial gastrectomy patients.^{1–3} Using different methods (x rays, photonabsorptiometry, histological analysis of bone biopsy specimens, and biochemical markers of bone turnover), most investigators have classified the changes as osteopenic or osteomalacic, or both.^{4–7} The precise diagnosis of osteomalacia, however, relies on bone histomorphometric analysis of bone specimens after tetracycline double labelling,⁸ where the demonstration of increased osteoid seam width as well as prolonged mineralisation lag time is mandatory.⁸ If the diagnosis is based solely on increased osteoid surface or increased

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TABLE I Results of serum biochemical tests in postgastrectomy patients and control subjects matched by age and sex

	No	Postgastrectomy group Mean (SD)	Control Mean (SD)	p
Calcium (mmol/l)	61	2.43 (0.10)	2.49 (0.07)	<0.01
Phosphorus (mmol/l)	60	1.00 (0.18)	1.17 (0.17)	<0.01
Alkaline phosphatase (U/l)	60	186 (72)	147 (34)	<0.01
25-hydroxyvitamin D (μ g/l)	66	17.3 (11.7)	27.4 (10.3)	<0.01
1,25-dihydroxyvitamin D (ng/ml)	65	41.9 (25.0)	30.6 (10.3)	<0.01

TABLE II Serum 25(OH)D concentrations (μ g/l) in postgastrectomy patients and control subjects with and without vitamin D supplementation

	No	Postgastrectomy patients Mean (SD)	Control Mean (SD)	p
Vitamin D supplement	40	21.8 (12.0)	35.5 (11.7)	<0.01
No supplement	28	11.7 (6.5)	18.1 (8.4)	<0.01

BONE HISTOMORPHOMETRY

Transcortical iliac crest bone biopsies were performed after tetracycline double labelling (labelling interval 10 days). Using light microscopy and fluorescence microscopy for tetracycline derived parameters the following indices were assessed according to standard techniques previously reported^{13 14 16} using a Zeiss II integrating grid and a computerised digitiser (Kontron, Germany). Only 51 biopsy specimens were suitable for estimating trabecular bone volume, 58 were suitable for determining static variables, and 46 for determining dynamic (tetracycline based) variable. (i) *Cancellous bone volume* (%): number of points hitting trabeculae divided by the total number of points hitting the section. (ii) *Erosion surface* (%): number of intersections with Howship lacunae divided by the total number of intersections with the trabecular surface. (iii) *Osteoid surface* (%): number of intersections with osteoid covered surface divided by the total number of intersections with the trabecular surface. (iv) *Thickness of osteoid seams* (μ m): mean of the osteoid width intercept distribution corrected for obliquity of the section plane by multiplying by $\pi/4$.¹³ (v) *Double labelled surface* (%): number of intersections with tetracycline double-labelled surface divided by the total number of intersections with trabecular surface. (vi) *Mineral appositional rate* (μ m/day): mean of four equidistant intercepts between the tetracycline double labels $\times \pi/4$. This index gives the mean apposition of bone mineral per unit time at actively mineralising surfaces. (vii) *Adjusted appositional rate* (μ m/day): mineral appositional rate \times (double labelled surface/formation surface). This index gives the mineral appositional rate averaged over the entire osteoid surface. (viii) *Mineralisation lag time* (days): thickness of osteoid seams/adjusted appositional rate. This index gives the mean period necessary to fully mineralise osteoid seams.

VITAMIN D ASSAYS

Serum 25-hydroxyvitamin D (25(OH)D = 25(OH)D₂ + 25(OH)D₃) was measured using a competitive binding assay¹⁵ with intra and interassay coefficients of variation of 3% and 14%, respectively. The detection limit was 0.8 μ g/l.

Serum 1,25-dihydroxyvitamin D (1,25(OH)₂D = 1,25(OH)₂D₂ + 1,25(OH)₂D₃) was measured using a competitive radioreceptor assay employing gut receptors from rachitic chicken.^{17 18} Intra and interassay coefficients of variation were both 11%. The detection limit was 6 ng/l.

OTHER BIOCHEMICAL ASSAYS

Serum calcium was measured using atomic absorptiometry and serum albumin was measured using an autoanalyser II (Technicon). Calcium was then corrected for individual variations in albumin. Serum alkaline phosphatase was measured using p-nitrophenylphosphate as substrate according to the recommendations of the Scandinavian Committee on Enzymes.¹⁹ Serum phosphate was measured using the molybdenum blue method.

STATISTICS

Differences between groups were tested using the Wilcoxon and Mann-Whitney tests for paired comparisons. The significance levels were set at 0.05.

Linear regression analysis was performed using the statistics pack from Hewlett-Packard. To secure homogeneity of variance logarithmic transformations were carried out when necessary. Based on significance testing of the coefficients in the multiple linear regression equation the relative contributions of the different determinants were evaluated.²⁰ In accordance with the general guidelines for evaluating multiple linear regression analyses $p < 0.10$ was considered significant.²⁰

Results

BIOCHEMISTRY

Serum concentrations of calcium and phosphate were lower in postgastrectomy patients, while serum alkaline phosphatase was increased (Table I). Serum concentrations of 25(OH)D were reduced, but 1,25(OH)₂D was increased in the postgastrectomy group. In two patients 25(OH)D concentrations were below the detection limit of the assay. Table II shows that the groups receiving multivitamin preparations containing 400–600 IU of D₂ had significantly higher 25(OH)D concentrations than those receiving no supplements. The control group had higher concentrations than the postgastrectomy group whether or not they were taking supplements.

BONE HISTOMORPHOMETRY

Compared with control subjects postgastrectomy patients had a lower trabecular bone volume and a greater osteoid seam thickness (Table III). The mineral appositional rate and adjusted appositional rate were the same in the two groups (Table III), while the mineralisation lag time was much longer in the postgastrectomy group.

Table IV gives the correlations between biochemical variables and histomorphometric indices. No correction for multiple comparison

TABLE III Histomorphometric indices in postgastrectomy patients and control subjects matched by age and sex

	No	Postgastrectomy patients Mean (SD)	Control subjects Mean (SD)	p
Trabecular bone volume (%)	51	15.3 (4.2)	19.3 (6.1)	<0.01
Osteoid surface (%)	59	21.4 (14.0)	18.6 (6.7)	NS
Erosion surface (%)	59	4.8 (2.3)	4.1 (1.3)	NS
Osteoid thickness (µm)	59	15.2 (4.6)	10.2 (2.8)	<0.01
Mineral appositional rate (µm/day)	46	0.60 (0.18)	0.65 (0.12)	NS
Adjusted appositional rate (µm/day)	46	0.47 (0.23)	0.50 (0.20)	NS
Mineralisation lag time (days)	46	99 (319)	24 (13)	<0.01

NS=not significant.

TABLE IV Correlation matrix between serum biochemical results and histomorphometric indices

	Osteoid surface	Erosion surface	Osteoid thickness	Mineral appositional rate	Adjusted appositional rate	Mineralisation lag time
Calcium	-0.51‡	-0.26	-0.46‡	0.35*	0.44‡	-0.54‡
Phosphate	0.01	-0.07	-0.16	0.23	0.18	-0.29
Alkaline phosphatase	0.40‡	0.25	0.61‡	-0.32*	-0.09	0.68‡
25-hydroxy-vitamin D	-0.37‡	-0.32*	-0.26*	0.18	0.32*	-0.32*
1,25-dihydroxy-vitamin D	-0.13	-0.03	-0.09	0.01	0.12	-0.08

*p<0.05; †p<0.01; ‡p<0.001.

was carried out. Serum calcium was positively correlated to mineral appositional rate and adjusted appositional rate, and inversely correlated to osteoid surface, osteoid thickness, and mineralisation lag time. Serum alkaline phosphatase showed a positive correlation to osteoid surface, osteoid thickness, and mineralisation lag time, and an inverse correlation to mineral appositional rate. 25-hydroxyvitamin D was positively correlated to adjusted appositional rate and inversely correlated to osteoid surface, osteoid thickness, erosion surface, and mineralisation lag time. No significant correlations to histomorphometry were demonstrable for 1,25-dihydroxyvitamin D or phosphate.

A patient was defined as having osteomalacia when the mineralisation lag time and osteoid thickness deviated more than 2 standard deviations (SD) from the mean of controls. Using this definition, eight of the 45 postgastrectomy patients (18%) (five of 27 in the polyga group, one of 13 in the Billroth I group, and two of five in the total gastrectomy group) were found to have osteomalacia. If the most widely used criterion, which is based on the presence of increased osteoid thickness only, had been applied 25 of the 45 patients (56%) would have been classified as having osteomalacia. If increased osteoid surface was used as the only criterion, 28 of the

45 patients (62%) would have been considered to have osteomalacia. Eleven of 46 patients (24%) had a significantly prolonged mineralisation lag time.

In six of the eight patients with osteomalacia, where all biochemical results were available, values for serum calcium and alkaline phosphatase were within the normal range. Moreover, in five of the eight 25(OH)D was in the normal range (Table V).

To test determinants for the development of a mineralisation defect after gastrectomy a multiple linear regression analysis was performed (Table VI). Age was the strongest determinant (p<0.01) followed by the 25(OH)D concentration (p<0.02) and observation period (p<0.10). No significant correlation was found between age or observation period and serum 25(OH)D concentrations (r=0.05 and r=0.01, respectively).

Discussion

This study showed that 18% of postgastrectomy patients had osteomalacia and in 24–62% of patients there were other abnormalities of bone remodelling depending on the parameter studied. The postgastrectomy patients showed reduced serum concentrations of calcium, phosphate, and 25(OH)D, while alkaline phosphatase and serum 1,25(OH)₂D were high. These findings are in accordance with those in previous studies.²¹ Some of the changes probably reflect compensatory mechanisms of calcium homeostasis in the form of a secondary hyperparathyroidism, which was initiated to compensate for the decreased vitamin D absorption and resulting calcium malabsorption previously shown in postgastrectomy patients, ileal bypass procedures for obesity, and resections in Crohn's disease.^{22,23} Thus in the early stages of osteomalacia increased circulating concentrations of parathyroid hormone mediate the stimulation of bone turnover with increases in resorption and formation surface.^{24,25} The more advanced stages of osteomalacia are characterised by low turnover. This is probably caused by most of the trabecular surface being covered by osteoid, thus preventing osteoclastic resorption.²⁶ In advanced forms of osteomalacia osteoblasts may also suffer from the severe 1,25(OH)₂D depletion due to decreased recruitment of osteoclastic and osteoblastic precursors. This is seen in the late stages of osteomalacia, where the wide osteoid seams are covered by inactive looking osteoblasts. Most patients with osteomalacia present a mixture of changes in bone remodelling ranging from secondary hyperparathyroidism in some areas of bone to frank osteomalacia in other areas.

The impairment of mineralisation as reflected by the duration of the mineralisation lag time correlated to the degree of vitamin D deficiency shown by serum 25(OH)D concentrations, but was unrelated to the serum concentrations of the biologically more active vitamin D analogue 1,25(OH)₂D. Mineralisation lag time also correlated to serum alkaline phosphatase, which is the standard serum marker for osteomalacia, and to the degree of hypocalcaemia as expressed in serum calcium. Despite these significant correla-

TABLE V Serum biochemical results in eight patients with osteomalacia as assessed by dynamic histomorphometry

Patient No	Calcium (mmol/l)	Alkaline phosphatase (U/l)	25(OH)D (µmol/l)	1,25(OH) ₂ D (ng/l)
1	2.37	192	14.4	37.7
2	2.43	139	15.3	85.3
3	2.37	222	8.0*	33.3
4	2.57	186	12.3	44.9
5	2.26*	317*	3.3*	23.1
6	2.31	128	11.3	90.4
7	2.10*	513*	0*	33.2
8	2.38	179	16.9	36.6

*Values outside 95% confidence intervals.

TABLE VI Determinants for the impairment of mineralisation in a population of 40 postgastrectomy patients as assessed by multiple linear regression

Equation: Mineralisation lag time=	$a_1 \times \text{serum } 25(\text{OH})\text{D} + a_2 \times \text{age} + a_3 \times \text{observation period} + c$
Coefficients:	$a_1 = -11.2 \text{ p} < 0.01$
	$a_2 = 14.6 \text{ p} < 0.02$
	$a_3 = 16.0 \text{ p} < 0.10$

tions, most of the patients with osteomalacia had normal serum alkaline phosphatase, calcium, 25(OH)D, and 1,25(OH)₂D. These results suggest that the high levels of alkaline phosphatase reflect the degree of secondary hyperparathyroidism in these patients rather than the degree of osteomalacia. Moreover, the results underscore the need for histological analysis, despite the presence of normal biochemical results, in patients suspected of having osteomalacia.

The prevalence of osteomalacia estimated in this population is similar to that reported in earlier histomorphometric studies,⁹⁻¹² but lower than the numbers given when the diagnosis was based on x ray, photonabsorptiometry, or biochemistry.^{4,5}

Vitamin D precursors are provided in food or through ultraviolet radiation of skin, and osteomalacia in postgastrectomy patients has been related to their nutritional state. Morgan *et al.*²⁵ reported osteomalacia in 23 total gastrectomy patients on a mean intake of 110 IU of vitamin D/day, while the intake in 27 total gastrectomy patients with no signs of metabolic bone disease was 186 IU/day. The intake of vitamin D in our postgastrectomy patients was the same as that in the control subjects, and no correlation between the histomorphometric indices for osteomalacia and general metabolic state was found.²⁶ Consequently, the osteomalacia in our group of postgastrectomy patients must be ascribed to reduced absorption of vitamin D from the gut.

The increased concentrations of 1,25(OH)₂D in this study are probably explained by increased 1- α -hydroxylase activity in the kidney mediated by parathyroid hormone and hypophosphataemia.²⁷⁻²⁹ Other studies have reported normal or even decreased concentrations of 1,25(OH)₂D, which may reflect differences in 1- α -hydroxylase activity or different degrees of 25(OH)D depletion.

The reduction in bone mass reported in several studies¹⁻⁵ is primarily attributable to the secondary hyperparathyroidism preceding the state of manifest osteomalacia. Secondary hyperparathyroidism leads to bone loss by three different mechanisms which often work in concert: (i) increased activation of resorptive cells leading to expansion of the remodelling space^{13,30}; (ii) a net negative balance per remodelling cycle; and (iii) resorption lacunae penetrating through trabeculae leading to perforation of the trabecular structure and irreversible bone loss.³¹ In osteomalacia bone turnover levels off, and thus bone loss is profoundly reduced. The changes in bone remodelling reported in this paper explain the increased risk of fracture in postgastrectomy patients, and emphasises the need for diagnosis, prophylaxis, and treatment of metabolic bone disease. The direct significant

correlation between 25(OH)D concentrations and degree of osteomalacia suggest that vitamin D supplementation is the most reasonable prophylaxis and treatment in these patients. Four of the eight patients, however, received vitamin D supplementation of 400–600 IU/day. Obviously this is too small a dose to prevent osteomalacia in a certain subgroup of patients.

The limited value of serum biochemical results in the diagnosis of osteomalacia is clearly shown in this study. As the diagnosis relies on bone histomorphometry and may be easily missed 10 to 20 years after surgery, it is probably wise to put all postgastrectomy patients on vitamin D supplements (two multivitamin tablets a day). In areas with a low habitual calcium intake, calcium supplementation may also be warranted. If a general prophylactic regimen for all postgastrectomy patients is not wanted, at least a follow up determination of serum alkaline phosphatase is needed. The multiple regression analysis suggests that increasing age and long duration of the postgastrectomy state are significant determinants. Thus such patients should be considered at high risk. Serial determinations of alkaline phosphatase will probably pick up the vast majority of cases with secondary hyperparathyroidism before they proceed to osteomalacia. If, however, osteomalacia is suspected due to the history or clinical symptoms – for example, low energy fractures, abnormal nutrition or malnutrition, malabsorption, skeletal pain, muscular pain, and weakness – a bone biopsy should be performed despite normal serum biochemistry.

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